Vitamin D and diabetes: A hypothesis still lacking credible proof

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Vitamin D research remains a hot topic. There are multiple observational studies linking low serum 25-hydroxyvitamin D (25[OH]D) concentrations to a multitude of disease outcomes including diabetes, as well as numerous mechanisms potentially explaining such associations. These observations have fuelled a frenzy of research activity, and the lay media has frequently reported "hot" vitamin D research findings. In the midst of this, a self-styled "Vitamin D Council" has been established (www.vitamindcouncil.org). Requests for 25(OH)D measurement are also rapidly expanding, particularly in primary care with demand often exceeding laboratory capabilities. Many researchers advocate the "correction" of vitamin D deficiency in several conditions such as rheumatoid arthritis and other chronic diseases. However, the data are not all consistent with some potential major "holes" in the vitamin D story. For example, although many studies report that low vitamin D levels predict incident diabetes, some do not.

The present report (Robinson et al, 2011; summarised alongside) from the US National Institutes of Health Women's Health Initiative related baseline serum 25(OH)D levels, albeit measured by the DiaSorin method and not the gold-standard approach of liquid chromatography/mass spectrometry, to risk of incident type 2 diabetes in 5140 women, of whom 317 developed type 2 diabetes over 7.3 years. The authors reported no significant association of 25(OH)D concentrations with incident diabetes in either age-adjusted or any other adjusted models.

Likewise, Makgoba et al (2011) also recently reported no significant association of antenatal visit-booking 25(OH)D concentrations with incident gestational diabetes in a large cohort of pregnant women in the UK.

As a result, both the authors of the present report and Makgoba et al have cautioned in making any recommendations about the need for vitamin D supplementation in the prevention of diabetes until results of ongoing studies have been revealed.

As reported previously in *Diabetes Digest*, current, small-scale studies on vitamin D supplementation in diabetes do not show any real benefit in terms of glycaemia, but doses used may have been too low (Sattar, 2010). One large, ongoing study – the VITAL (Vitamin and Omega-3 Trial) – is testing the benefits of vitamin D 2000 IU/day over 5 years in >20 000 men and women against a range of outcomes, with diabetes being one of the pre-specified secondary endpoints (www.vitalstudy.org). There are also other large-scale studies being planned.

Given the inconsistencies of epidemiological data in this area, as well as potential for residual confounding and reverse causality (Welsh et al, 2011), we must await the results of these trials before making any recommendations on vitamin D supplementation in diabetes management. Interestingly, a report by the Institute of Medicine of the National Academies (Ross et al, 2010) supports this approach and went even further: "The committee … found that the evidence supported a role for these nutrients [calcium and vitamin D] in bone health but not in other health conditions … the majority of Americans and Canadians are receiving adequate amounts of both calcium and vitamin D. Further, there is emerging evidence that too much of these nutrients may be harmful."

Therefore, the vitamin D hypothesis in diabetes remains just that; physicians should generally avoid making requests for blood vitamin D measurements outside of the bone health area.

Makgoba M, Nelson SM, Savvidou M et al (2011) First-trimester circulating 25-hydroxyvitamin D levels and development of gestational diabetes mellitus. *Diabetes Care* **34**: 1091–3

Ross AC, Taylor CL, Yatkine AL et al (2010) *Dietary Reference Intakes for Calcium and Vitamin D*. Food and Nutrition Board, Institute of Medicine of the National Academies, Washington, DC. Available at: http://bit.ly/hK2KJS (accessed 31.05.11)

Sattar N (2010) Vitamin D deficiency as a cause of diabetes? A critique of the current evidence base. *Diabetes Digest* **9**: 204

Welsh P, Peters MJ, Sattar N (2011) Vitamin D insufficiency. *N Engl J Med* **364**: 1378–9

DIABETES CARE

No association between vitamin D levels and T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Previous studies have reported inverse associations between vitamin D and incident diabetes, but data have been inconsistent.

2 The authors of this study investigated whether low levels of serum 25-hydroxyvitamin D (25[OH]D) are associated with an increased risk of incident T2D.

3 This was a *post hoc* analysis of data from three nested case–control studies assessing 25(OH)D levels in women who were participants of the Women's Health Initiative clinical trials with no baseline diabetes.

4 The study population consisted of 5140 women aged 50–79 years (mean age 66 years) who were followed-up for a mean of 7.3 years.

5 During follow-up, 317 women (6.2%) developed T2D.

6 A possible trend toward lower risk of T2D was associated with increasing serum 25(OH)D quartiles (<34.7 nmol/L, 34.7–47.8 nmol/L, 47.9–64.2 nmol/L and >64.2 nmol/L); however, after adjustments for a number of risk factors, the association attenuated to the null (odds ratio, 1.01; *P* for trend=0.94).

7 Furthermore, there was no linear association found between 25(OH)D levels, using clinical cut-points (<50 nmol/L, 50–74 nmol/L and ≥75 nmol/L) or a continuous model (5-nmol/L increments), and T2D risk.

8 In this population of postmenopausal women, no association was found between low serum 25(OH)D levels and increased risk of developing T2D.

Robinson JG, Manson JE, Larson J et al (2011) Lack of association between 25(OH)D levels and incident type 2 diabetes in older women. *Diabetes Care* **34**: 628–34

DIABETOLOGIA

Fenofibrate reduces loss of renal function and albuminuria

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The authors investigated the effects of long-term fenofibrate use on renal outcomes in the previously conducted FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study.

2 A total of 9795 participants with T2D (aged 50–75 years) were randomised to receive fenofibrate 200 mg/day (n=4895) or placebo (n=4900) for approximately 5 years.

3 Urinary albumin:creatinine ratio (ACR) was measured at baseline, year 2, year 5 and close-out. The estimated glomerular filtration rate (eGFR) was measured every 4–6 months.

4 Plasma creatinine levels were re-measured 8 weeks after close-out in 661 participants – the washout substudy.

5 Plasma creatinine levels were higher in the fenofibrate arm than in the placebo arm but the increase was slower, with an annual increase of 1.62 µmol/L vs 1.89 µmol/L).

6 The rate of eGFR decline was also slower among the fenofibrate group (annual rate of 1.19 vs 2.03 mL/min/1.73 m^2).

7 Urinary ACR was reduced in both treatment groups but this was greater in the fenofibrate group (23.7% vs 11.5% in the placebo group; mean difference 13.9%; P<0.001).

8 The authors concluded that fenofibrate treatment reduced albuminuria progression and loss of renal function over 5 years.

Davis TM, Ting R, Best JD et al (2011) Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* **54**: 280–90

DIABETES

Triglyceride-raising SNPs show no risk of influencing T2D

Readability	✓✓✓✓
Applicability to practice	✓
WOW! factor	✓✓✓

1 The aim of this study was to determine if the association between increased triglyceride levels and T2D and insulin resistance is causal.

2 Ten triglyceride-raising single-nucleotide polymorphisms (SNPs) were studied in 12 497 individuals (5637 with T2D and 6860 controls). In addition, continuous-outcome variables (fasting glucose, fasting insulin, HOMA-B and HOMA-IR) were assessed in 8271 individuals without diabetes from four studies.

3 There was no association between T2D and any SNPs and no evidence that individuals carrying a greater number of the triglyceride-raising alleles were at higher risk of developing T2D.

4 Only one allele showed positive association with fasting insulin (P=0.004) and HOMA-IR (P=0.004).

5 It was concluded that increased triglycerides did not increase the risk of T2D or influence fasting insulin levels and insulin resistance.

De Silva NM, Freathy RM, Palmer TM et al (2011) Mendelian randomization studies do not support a role for raised circulating triglyceride levels influencing type 2 diabetes, glucose levels, or insulin resistance. *Diabetes* **60**: 1008–18

DIABETOLOGIA

Increased prevalence of NAFLD in women with previous GD

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 The prevalence of non-alcoholic fatty liver disease (NAFLD) in European women with previous gestational diabetes (GD) was studied.

2 Using data from antenatal care databases, the authors compared lipid levels and insulin sensitivity and secretion in 110 women with previous GD and 113 women without.

3 Women with previous GD had higher insulin secretion (HOMA-B 97% vs 64%; P<0.001) and lower insulin sensitivity (HOMA-S 89% vs 154%; P<0.001) than women without.

4 The prevalence of NAFLD was significantly greater among women with previous GD (38% vs 17%; P=0.001), as was the prevalence of dyslipidaemia.

5 The authors concluded that reduced insulin sensitivity and increased serum alanine transaminase levels were closely associated with NAFLD in these women with previous GD.

Forbes S, Taylor-Robinson SD, Patel N et al (2011) Increased prevalence of non-alcoholic fatty liver disease in European women with a history of gestational diabetes. *Diabetologia* **54**: 641–7

DIABETES CARE

Bariatric surgery reduces renal and CV complications

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 The authors sought to determine the effect of bilio-pancreatic diversion (BPD) on cardiovascular (CV; micro- and macrovascular) outcomes in an obese population (BMI >35 kg/m^2) with new onset T2D.

2 A total of 50 obese people with newly diagnosed T2D participated: 22 underwent conventional medical therapy and 28 underwent BPD surgery.

3 After 10 years, glomerular filtration rate declined by 45.7% in the medical therapy arm and increased by 13.6% in the surgical arm (P<0.001).

4 The risk of coronary heart disease was found to be greater in the medical arm at 10-year follow-up (0.22% vs 0.05% in the surgical group; P<0.001).

Iaconelli A, Panunzi S, De Gaetano A et al (2011) Effects of bilio-pancreatic diversion on diabetic complications. *Diabetes Care* **34**: 561–7

"The prevalence of non-alcoholic fatty liver disease was significantly greater among women with previous gestational diabetes, as was the prevalence of dyslipidaemia."

"... apolipoproteins were more significantly associated with diabetic retinopathy than traditional lipids and were better able to discriminate diabetic retinopathy."

DIABETES

Serum VAP-1 improves mortality risk prediction in T2D

Readability	✓✓✓✓
Applicability to practice	✓
WOW! factor	✓✓

1 The authors investigated whether vascular adhesion protein-1 (VAP-1) can be used to predict 10-year survival in people with T2D.

2 A total of 661 individuals with T2D were enrolled and serum VAP-1 levels were measured; participants were followed for a median of 10.4 years.

3 Participants with VAP-1 levels in the highest tertile (≥780 ng/mL) had an adjusted hazard ratio (HR) of 2.19 (95% confidence interval, 1.17–4.11; $P<0.05$) for 10-year all-cause mortality.

4 The HRs for 1-unit change in natural log VAP-1 for disease-specific mortality were 5.83 for cardiovascular disease (CVD), 9.71 for diabetes, 6.32 for CVD and diabetes and 17.24 for cancer (all $P\leq0.05$).

5 The authors concluded that serum VAP-1 can predict 10-year mortality in T2D.

Li HY, Jiang YD, Chang TJ et al (2011) Serum vascular adhesion protein-1 predicts 10-year cardiovascular and cancer mortality in individuals with type 2 diabetes. *Diabetes* **60**: 993–9

DIABETES CARE

Association between dietary patterns and incident T2D in Singapore

Readability	✓✓✓✓
Applicability to practice	✓
WOW! factor	✓✓✓

1 The aim of this study was to examine dietary patterns and their associations with incident T2D.

2 Data from the Singapore Chinese Health Study for 43 176 men and women (aged 45–74 years) without diabetes at baseline were assessed.

3 A total of 246 898 person-years were accumulated, in which time 2252 individuals (5.2%) developed T2D.

4 Two dietary patterns were identified: a vegetable, fruit and soy-rich (VFS) and a dim sum and meat-rich (DSM) pattern.

5 Neither pattern was associated with T2D risk in smokers (n=11 850).

6 Among never smokers (n=31 326), a significant inverse association was seen with VFS intake and a positive association was seen with DSM intake.

7 A higher intake of DSM food was found to increase the risk of T2D in Chinese men and women.

Odegaard AO, Koh WP, Butler SD et al (2011) Dietary patterns and incident type 2 diabetes in Chinese men and women. *Diabetes Care* **34**: 880–5

DIABETES CARE

Osteoprotegerin predicts all-cause and CVD mortality

Readability	✓✓✓✓
Applicability to practice	✓
WOW! factor	✓✓✓

1 Osteoprotegerin (OPG) – produced by vascular smooth muscle cells – is thought to be a strong, independent predictor of cardiovascular disease (CVD) in high-risk individuals.

2 In this study, the use of OPG in predicting all-cause and CV mortality risk in 283 people with T2D was investigated.

3 During the median follow-up of 16.8 years, 193 participants (68%) died, including 103 (36%) from CVD.

4 The highest third of OPG level compared with the lowest predicted all-cause mortality with a hazard ratio (HR) of 1.81 (P=0.005).

5 High and medium OPG levels versus low levels predicted CV mortality (HRs 3.51 and 1.86, respectively).

6 The authors concluded that raised OPG levels are a strong predictor of all-cause mortality in T2D.

Reinhard H, Lajer M, Gall MA et al (2010) Osteoprotegerin and mortality in type 2 diabetic patients. *Diabetes Care* **33**: 2561–6

DIABETES CARE

Apolipoproteins strong biomarkers of diabetic retinopathy

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Traditional measures of serum lipids (e.g. triglycerides) have been shown to be positively associated with diabetic retinopathy (DR), but not consistently.

2 The authors compared the associations of traditional serum lipids (total, LDL, HDL and triglycerides) and apolipoproteins (apoAI, apoB, and the apoB:ApoAI ratio) with DR in people with diabetes.

3 The study population consisted of 224 adults (aged 18–70 years) with diabetes: 85 with T1D and 139 with T2D.

4 DR, as determined from retinal photography, was present in 133 participants: 31 with mild, 50 with moderate and 52 with vision-threatening DR.

5 Blood samples were taken to assess lipid levels 2 weeks after the eye examinations.

6 Of the traditional lipids, only HDL was inversely associated with DR (odds ratio [OR], 0.39 for highest versus lowest quarter).

7 Per standard deviation increase, apoAI, apoB and the apoB:apoAI ratio were all strongly correlated with DR (OR, 0.76, 1.31 and 1.48, respectively).

8 Area under the curve for predicting DR was improved by the traditional lipids by 1.8% compared with 8.2% with the apolipoproteins.

9 The authors concluded that the apolipoproteins were more significantly associated with DR than traditional lipids and were better able to discriminate DR, and thus may be stronger biomarkers.

Sasongko MB, Wong TY, Nguyen TT et al (2011) Serum apolipoprotein AI and B are stronger biomarkers of diabetic retinopathy than traditional lipids. *Diabetes Care* **34**: 474–9